**antigens)**

L13 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:546956 CAPLUS
DOCUMENT NUMBER: 122:274119
TITLE: Hydrophobic polymeric pharmaceutical microparticles
INVENTOR(S): Andrianov, Alexander K.; Langer, Robert S.
PATENT ASSIGNEE(S): Virus Research Institute, USA; Massachusetts Institute of Technology
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9508320 | A1 | 19950330 | WO 1994-US10692 | 19940921 |
| W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, UZ, VN | | | | |
| RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5500161 | A | 19960319 | US 1993-124816 | 19930921 |
| CA 2172040 | AA | 19950330 | CA 1994-2172040 | 19940921 |
| AU 9478001 | A1 | 19950410 | AU 1994-78001 | 19940921 |
| EP 720471 | A1 | 19960710 | EP 1994-928640 | 19940921 |
| EP 720471 | B1 | 20010418 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |

PRIORITY APPLN. INFO.: US 1993-124816 A 19930921
WO 1994-US10692 W 19940921

AB A method for the prepn. of microparticles, and the product thereof, that include dispersing a substantially water insol. non-ionic or ionic polymer in an aq. soln. in which the substance to be delivered is also dissolved, dispersed or suspended, and then coagulating the polymer together with the substance by impact forces to form a microparticle. In an alternative embodiment, the microparticle is formed by coagulation of an aq. polymeric dispersion through the use of electrolytes, pH changes, org. solvents in low concns. (the minimal amt. necessary to break up the dispersion), or temp. changes to form polymer matrixes encapsulating biol. materials. Thus 60 mg of fluorescein-labeled bovine serum albumin was dissolved in 3 mL of 30% aq. soln. dispersion of Eudragite NE 30D and then spraying the aq. dispersion in a flask contg. 200 mL of deionized water using

Turbotack air-atomizing nozzle. The flow rate of the polymeric dispersion was 150.mu.L/min, the air pressure was 25 psi, and the distance between the nozzle and surface of water was 30 cm. The resulting microparticles were spherical with an av. diam. of 1-10 .mu.m and encapsulation efficiency of 65%.

IT **34346-01-5**, **Glycolic** acid-**lactic** acid copolymer
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrophobic polymeric pharmaceutical microparticles)

L13 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:467421 CAPLUS
DOCUMENT NUMBER: 122:222580
TITLE: Adjuvanticity and protective immunity elicited by Bordetella **pertussis** **antigens** encapsulated in **poly**(**DL-lactide**-co-**glycolide**) microspheres
AUTHOR(S): Shahin, Roberta; Leef, Mary; Eldridge, John; Hudson, Michael; Gilley, Richard
CORPORATE SOURCE: Lab. Pertussis, Cent. Biol. Eval., Bethesda, MD, USA
SOURCE: Infect. Immun. (1995), 63(4), 1195-200
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purified Bordetella **pertussis** **antigens**, encapsulated in biodegradable **poly**(**DL-lactide**-co-**glycolide**) (DL-**PLG**) microspheres, were evaluated for their immunogenicity and ability to elicit a protective immune response against B. **pertussis** respiratory infection. Microencapsulated **pertussis** toxoid, filamentous hemagglutinin, and pertactin all retained their immunogenicity when administered parenterally. Intranasal immunization with a low dose (1 .mu.g) of encapsulated filamentous hemagglutinin, **pertussis** toxoid, or pertactin elicited strong specific IgG and IgA antibody responses in respiratory secretions that were greater in magnitude than the responses elicited by the same doses of unencapsulated **antigen**. Intranasal immunization with as little as 1 .mu.g of encapsulated **pertussis** **antigen** prior to infection reduced the bacterial recovery by 3 log130 CFU. However, intranasal immunization with the same low doses of unencapsulated **antigens** did not reduce infection. Intranasal administration of a combination of 1 .mu.g of ech of the microencapsulated **pertussis** **antigens** was more effective in reducing bacterial infection than administration of any single microencapsulated **antigen**. Intranasal

administration of microencapsulated B. **pertussis antigens** elicits high levels of specific antibody coinciding with protection against infection when these microspheres are administered to the respiratory tract. These data provide evidence of the respiratory adjuvanticity of three different DL-PLG microsphere prepns., each of which contains a unique b. **pertussis antigen**.

IT **26780-50-7**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adjuvanticity and protective immunity by Bordetella **pertussis antigens** encapsulated in **poly** (**DL-lactide**-co-**glycolide**) microspheres)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, TOXLIT, TOXLINE, PHIC, PHIN' ENTERED AT 15:06:47 ON 04 JUN 2001)

L14 31 S L12
L15 23 S L14 NOT L9
L16 17 DUP REM L15 (6 DUPLICATES REMOVED)

L16 ANSWER 1 OF 17 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-205407 [18] WPIDS
DOC. NO. CPI: C2000-063253
TITLE: Microparticles with adsorbent surface comprising polymer and detergent, used as vaccines, and for targeted delivery of e.g. polypeptides, efficient adsorbance of biologically active macromolecules.
DERWENT CLASS: A14 A23 A26 A96 B04 B07 C03 D16
INVENTOR(S): BARACKMAN, J; KAZZAZ, J; O'HAGEN, D; OTT, G S; SINGH, M
PATENT ASSIGNEE(S): (CHIR) CHIRON CORP
COUNTRY COUNT: 87
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2000006123 | A1 | 20000210 | (200018)* | EN | 59 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW | | | | | |
| W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW | | | | | |
| AU 9952452 | A | 20000221 | (200029) | | |
| EP 1100468 | A1 | 20010523 | (200130) | EN | |
| R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI | | | | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2000006123 | A1 | WO 1999-US17308 | 19990729 |
| AU 9952452 | A | AU 1999-52452 | 19990729 |
| EP 1100468 | A1 | EP 1999-937664 | 19990729 |
| | | WO 1999-US17308 | 19990729 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9952452 | A | Based on | WO 200006123 |
| EP 1100468 | A1 | Based on | WO 200006123 |

PRIORITY APPLN. INFO: US 1999-285855 19990402; US 1998-124533 19980729

AN 2000-205407 [18] WPIDS

AB WO 200006123 A UPAB: 20000412

NOVELTY - Microparticles with an adsorbent surface are new and comprise:

(1) polymer chosen from poly( alpha -hydroxy acid), polyhydroxy butyric acid, polycaprolactone, polyorthoester, polyanhydride or polycyanoacrylate; and

(2) detergent.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of producing microparticles with adsorbent surface to which biologically active macromolecule has been adsorbed.

ACTIVITY - Vaccine; immunomodulating. Microparticle induction of immune response was examined in guinea pigs following intramuscular immunization. Five formulations were tested: (1) PLG/CTAB gp 120 adsorbed (25 mu g); (2) PLG/CTAB gp 120 adsorbed (25 mu g) + aluminum phosphate; (3) soluble gp 120 DNA (25 mu g) + aluminum phosphate; (4) soluble gp 120 DNA (25 mu g) alone; and (5) MF59 protein (50 mg). GMT of serum was as follows: (1) 1,435 plus or minus 383; (2) 3,624 plus or minus 454; (3) 119 plus or minus 606; (4) 101 plus or minus 55; and (5) 3,468 plus or minus 911. Antibody induction (collection and analysis of serum) were performed and geometric mean titer of serum determined.

USE - Used for diagnosis or treatment of disease, as vaccines and to raise and immune response. Used to deliver polypeptides, polynucleotides, polynucleosides, **antigens**, pharmaceuticals, hormones, enzymes, transcription or translation mediators, intermediates in metabolic pathway, immunomodulators or adjuvants including aluminum salts (claimed) such as double- and single stranded sequences including cDNA, prokaryotic or eukaryotic mRNA, genomic RNA and DNA sequences form viral or prokaryotic DNA

(RNA and DNA viruses), and synthetic DNA sequences, base analogs of DNA and RNA, antibiotics, antivirals, peptides, oligopeptides, dimers, multimers, **antigens** derived from bacteria (Bordetella **pertussis**, Neisseria meningitides (A, B, C, Y), Neisseria gonorrhoeae, Helicobacter pylori and/or Haemophilus influenzae), viruses, parasites, fungi and tumors, non-steroidal anti-inflammatory drugs, analgesics, vasodilators, cardiovascular drugs, psychotropics, neuroleptics, antidepressants, anti-Parkinson drugs, beta blockers, calcium channel blockers, bradykinin inhibitors, angiotensin-converting enzyme inhibitors, prolactin inhibitors, steroids, hormone antagonists, antihistamines, serotonin antagonists, heparin, chemotherapeutic agents, antineoplastics and growth factors (platelet derived growth factor (PDGF), epithelial growth factor (EGF), KGF, insulin-like growth factor (IGF)-1, IFG-2), FGF, polynucleotides that encode therapeutic or immunogenic proteins, immunogenic proteins and epitopes for use in vaccines, hormones including peptide hormones (insulin, proinsulin, growth hormone, GHRH, luteinizing hormone releasing hormone (LHRH), EGF, somatostatin, SNX-111, BNP, insulinotropin, ANP, FSH, LH, PSH and hCG), gonadal steroid hormones (androgens, estrogens, progesterone), thyroid-stimulating hormone, inhibin, cholecystokinin, ACTH, CRF, dynorphins, endorphins, endothelin, fibronectin fragments, galanin, gastrin, glucagons, GTP-binding protein fragments, guanylin, leukokinins, magainin, mastoparans, dermaseptin, systemin, neuromedin, neurotensin, pancreastatin, pancreatic polypeptide, substance P, secretin, thymosin, and cytokines (interleukin (IL) 1, IL-2, IL-3, IL-4 and gamma interferon). Used for site-specific targeted delivery.

ADVANTAGE - Efficiently adsorb biologically active macromolecules such as DNA, polypeptides, **antigens** and adjuvants. Capable of adsorbing wide variety of macromolecules. Flexible delivery systems, particularly for drugs that are highly sensitive and difficult to formulate.

Dwg.0/0

L16 ANSWER 2 OF 17 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-236702 [20] WPIDS

CROSS REFERENCE: 1988-121200 [18]; 1989-272277 [38]; 1996-189757 [20]; 1998-530832 [45]; 1998-541706 [46]; 1998-567595 [48]; 1999-094826 [08]; 1999-526186 [44]

DOC. NO. CPI: C2000-071978

TITLE: Microcapsule and **antigen** compositions for potentiating immune responses mediated by Peyer's patches and useful for vaccinating against a variety of allergens and microbial pathogens.

DERWENT CLASS: A96 B04 B07 D16

INVENTOR(S): ELDRIDGE, J H; GILLEY, R M; STAAS, J K; TICE, T R

PATENT ASSIGNEE(S): (SOUR) SOUTHERN RES INST; (UABR-N) UAB RES FOUND
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| US 6024983 | A | 20000215 | (200020)* | | 24 |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| US 6024983 | A | CIP of | US 1986-923159 | 19861024 |
| | | CIP of | US 1988-169973 | 19880318 |
| | | CIP of | US 1989-325193 | 19890316 |
| | | Cont of | US 1990-629138 | 19901218 |
| | | | US 1993-116802 | 19930907 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| US 6024983 | A | CIP of | US 5075109 |

PRIORITY APPLN. INFO: US 1990-629138 19901218; US 1986-923159 19861024; US 1988-169973 19880318; US 1989-325193 19890316; US 1993-116802 19930907

AN 2000-236702 [20] WPIDS

CR 1988-121200 [18]; 1989-272277 [38]; 1996-189757 [20]; 1998-530832 [45]; 1998-541706 [46]; 1998-567595 [48]; 1999-094826 [08]; 1999-526186 [44]

AB US 6024983 A UPAB: 20000426

NOVELTY - Microcapsule compositions comprising **antigens** for potentiating immune responses mediated by Peyer's patches (also called folliculi lymphatic aggregati), are new.

DETAILED DESCRIPTION - A composition (I) for potentiating an immune response in an animal, comprising 2 sets of biocompatible microcapsules (1 - 10 mu m in diameter) containing 2 bioactive agents encapsulated in biocompatible excipients. The first set of microcapsules (Ia) provide a primary immune response and the second set (Ib) releases it's bioactive agent in a pulsed manner to potentiate the subsequent immune response.

An INDEPENDENT CLAIM is also included for a method (II) of preparing (I).

ACTIVITY - Antimicrobial; immunostimulant.

MECHANISM OF ACTION - Vaccine adjuvant or synergist.

Research has shown that microencapsulation results in a profoundly heightened immune response to the incorporated

**antigen** or vaccine in numerous experimental systems. An example is provided by the direct comparison of the level and isotype distribution of the circulating antibody response to Staphylococcal enterotoxin B, the causative agent of Staphylococcal food poisoning. Following immunization with either soluble or microencapsulated enterotoxoid. Groups of mice were administered various doses of the toxoid vaccine incorporated in 50:50 **poly**(**DL**-**lactide**-co-**glycolide**) microcapsules, or in soluble form, by intraperitoneal (IP) injection. On Days 10 and 20 following immunization, plasma samples were obtained and assayed for antitoxin activity by end-point titration in isotype-specific immunoradiometric assays. The optimal dose of soluble toxoid (25 mu g) elicited a characteristically poor immune response to the toxin which was detected only in the immunoglobulin (Ig)-M isotype. In contrast, the administration of 25 mu g of toxoid incorporated within microcapsules induced not only an IgM response, but an IgG response which was detectable at a plasma dilution of 1/2560 on day 20 post immunization. In addition, larger doses of toxoid could be administered in microencapsulated form without decreasing the magnitude of the response, as was seen with a 50 mu g dose of soluble toxoid. In fact, the measured release achieved with the microcapsules allows for 4 - 5 times the dose to be administered without causing high zone paralysis, resulting in substantially heightened immunity. This adjuvant activity is even more pronounced following secondary and tertiary immunizations.

The Day 20 IgG antitoxin response following secondary immunization was 512 times higher in mice receiving 50 mu g of microencapsulated toxoid than in mice receiving the optimal dose of soluble toxoid. Further, tertiary immunization with the soluble toxoid at its optimal dose was required to raise an antibody response to the toxin which was equivalent to that observed following a single immunization with 100 mu g micrograms of microencapsulated enterotoxoid. Adjuvant activity of equal magnitude has been documented to common laboratory protein **antigens** such as haptenated keyhole limpet hemocyanin and influenza virus vaccine.

USE - (I) is used for delivering a bioactive agent that provides/potentiates an immune response in the mucosally associated lymphoreticular tissues (Peyer's patches) of an animal or for parenterally delivering a bioactive agent that potentiates an immune response (claimed). The composition may be used to induce systemic and mucosal immunity to the animal (claimed). The compositions may be used to vaccinate against allergens, viral **antigens**, bacterial **antigens**, protozoan **antigens** or fungal **antigens** such as influenzae **antigens**, Staphylococcus **antigens**, respiratory syncytial **antigens** parainfluenzae **antigens**, Hemophilus influenza **antigens** Bordetella **pertussis**

**antigens**, Neisseria gonorrhea **antigens**, Streptococcus pneumoniae **antigens**, Plasmodium falciparum **antigens**, helminthic pathogen **antigens** or **antigens** to vaccinate against allergies. In particular, it is used to vaccinate against influenza virus or Staphylococcal enterotoxin B (claimed).

ADVANTAGE - The microcapsules are capable of passing through the gastrointestinal tract without degradation (claimed). The size of the microcapsules allows them to pass through or be retained in mucosally associated lymphoreticular tissues (claimed). The use of (I) obviates the need for other immunopotentiators.

Dwg.0/4

L16 ANSWER 3 OF 17 TOXLIT
ACCESSION NUMBER: 2000:8406 TOXLIT
DOCUMENT NUMBER: CA-132-199031H
TITLE: Oral vaccine compositions.
AUTHOR: Brayden DJ
SOURCE: (2000). PCT Int. Appl. PATENT NO. 0012124 03/09/2000 (Elan Corporation, PLC).
CODEN: PIXXD2.
PUB. COUNTRY: IRELAND
DOCUMENT TYPE: Patent
FILE SEGMENT: CA
LANGUAGE: English
OTHER SOURCE: CA 132:199031
ENTRY MONTH: 200003

AB Oral vaccine formulations are disclosed having microparticles sized such that at least 50% of the microparticles are less than 5 .mu.m, preferably less than 3 .mu.m, the microparticles contg. **antigen** entrapped or encapsulated, e.g. by a solvent evapn. method, by a biodegradable polymer, e.g. **poly**(**D**, **L**-**lactide**-co-**glycolide**). Addnl., oral vaccine formulations are disclosed having nanoparticles sized such that at least 50% of the microparticles are less than 600 nm, preferably less than 500 nm, the nanoparticles contg. **antigen** entrapped or encapsulated, e.g. by a coacervation method, by a biodegradable polymer, e.g. **poly**(**D**, **L**-**lactide**-co-**glycolide**). Protective vaccine formulations contg. the B. **pertussis** **antigens** PTd or a combination of PTd and FHA are provided.

L16 ANSWER 4 OF 17 TOXLIT
ACCESSION NUMBER: 2000:127523 TOXLIT
DOCUMENT NUMBER: CA-134-212529Q
TITLE: Encapsulation of conjugate vaccines with Bordetella **pertussis** fimbriae as novel carrier proteins.
AUTHOR: Crowley-Luke A; Sims M; Reddin K; Vincent P; Gorringe

A; Hudson M; Robinson A
CORPORATE SOURCE: Centre for Applied Microbiology and Research, Salisbury
SOURCE: Proc. Int. Symp. Controlled Release Bioact. Mater., (2000). Vol. 27th, pp. 554-555.
CODEN: PCRMEY. ISSN. 1022-0178.
PUB. COUNTRY: UNITED KINGDOM
DOCUMENT TYPE: Journal; Journal Article
FILE SEGMENT: CA
LANGUAGE: English
OTHER SOURCE: CA 134:212529
ENTRY MONTH: 200103
AB B. **pertussis** fimbriae were used as carrier proteins to produce vaccine that would protect against Hib and augment protection induced against B. **pertussis** disease where acellular **pertussis** vaccines deficient in fimbriae are used. Poly(lactide-glycolide) was used for microencapsulation of **antigen**.

L16 ANSWER 5 OF 17 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999410154 EMBASE
TITLE: Protection against B. **pertussis** challenge following parenteral and oral administration of microparticles loaded with **pertussis antigens**.
AUTHOR: McClean S.; Conway M.; Mills K.H.G.; Brayden D.J.
CORPORATE SOURCE: D.J. Brayden, Elan Pharmaceutical Technologies, Trinity College, Dublin 2, Ireland
SOURCE: Proceedings of the Controlled Release Society, (1999) -/26 (153-154).
Refs: 4
ISSN: 1022-0178 CODEN: 58GMAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English

L16 ANSWER 6 OF 17 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999186488 EMBASE
TITLE: Single-administration vaccines: Controlled-release technology to mimic repeated immunizations.
AUTHOR: Cleland J.L.
CORPORATE SOURCE: J.L. Cleland, Pharmaceutical R and D, Genentech, 1

DNA Way, South San Francisco, CA 94080, United States. cleland@gene.com
SOURCE: Trends in Biotechnology, (1999) 17/1 (25-29).
Refs: 33
ISSN: 0167-7799 CODEN: TRBIDM
PUBLISHER IDENT.: S 0167-7799(98)01272-4
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The most effective mechanism for the elimination of disease from society is the use of vaccinations, but these often require repeated administration. However, single-administration vaccine formulations provide the repeated administrations automatically. One approach is the development of injectable controlled-release microsphere formulations containing the vaccine **antigen** that is released as a pulse 1-6 months after injection. The time of the pulse is dependent upon the rate of polymer degradation, which is dictated by the polymer's composition and molecular weight. This controlled-release technology may provide complete protection against disease after a single administration. Copyright (C) 1999 Elsevier Science Ltd.

L16 ANSWER 7 OF 17 TOXLIT
ACCESSION NUMBER: 1998:162948 TOXLIT
DOCUMENT NUMBER: CA-130-086184A
TITLE: Vaccines containing Bordetella **pertussis antigen.**
AUTHOR: Farrar GH; Jones DH
SOURCE: (1998). PCT Int. Appl. PATENT NO. 9858668 12/30/1998 (Microbiological Research Authority). CODEN: PIXXD2.
PUB. COUNTRY: UNITED KINGDOM
DOCUMENT TYPE: Patent
FILE SEGMENT: CA
LANGUAGE: English
OTHER SOURCE: CA 130:86184
ENTRY MONTH: 199902
AB A vaccinating conjugate comprises an **antigen** conjugated to a carrier selected from Bordetella **pertussis** fimbria, **pertussis** toxin, **pertussis** toxoid, and **pertussis** 69kD protein. The conjugate may also comprise a second **antigen**, different from the first. An oral vaccinating compn. comprises Bordetella **pertussis** fimbria or fimbria-**antigen** conjugate.

L16 ANSWER 8 OF 17 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999016458 EMBASE
TITLE: Approaches to new vaccines.
AUTHOR: Mahon B.P.; Moore A.; Johnson P.A.; Mills K.H.G.
CORPORATE SOURCE: B.P. Mahon, Infection and Immunity Group, National University of Ireland, Maynooth, County Kildare, Ireland
SOURCE: Critical Reviews in Biotechnology, (1998) 18/4 (257-282).
Refs: 161
ISSN: 0738-8551 CODEN: CRBTE5
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 026 Immunology, Serology and Transplantation
027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The explosive technological advances in the fields of immunology and molecular biology in the last 5 years had an enormous impact on the identification of candidate vaccines against diseases, which until a few years ago seemed uncontrollable. Increased knowledge of the immune system has helped to define the mechanisms that underlie successful immunization and is now being exploited to develop improved versions of existing vaccines and new vaccines against emerging pathogens, tumors, or autoimmune diseases. An understanding of the mechanisms of action of novel adjuvants and the development of new vector and delivery systems will have a major impact on vaccine strategies. The use of DNA encoding **antigens** from pathogenic viruses, bacteria, and parasites as vaccines is a new approach that is receiving considerable attention. This and other innovative approaches, including vaccine production in plants, are appraised in this review. The successful eradication of smallpox and the imminent eradication of poliomyelitis by worldwide immunization campaigns provide positive examples of how the vaccine-mediated approach can lead to disease elimination; with the advent of new vaccines and improved delivery systems, there is no scientific reason why these successes cannot be repeated.

L16 ANSWER 9 OF 17 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998131449 EMBASE
TITLE: Oral and nasal immunization with microencapsulated clinically relevant proteins.
AUTHOR: Alpar H.O.; Eyles J.E.; Williamson E.D.

CORPORATE SOURCE: H.O. Alpar, Pharmaceutical Sciences Institute, Aston University, Aston Triangle, Birmingham B4 7ET, United Kingdom
SOURCE: S.T.P. Pharma Sciences, (1998) 8/1 (31-39).
Refs: 73
ISSN: 1157-1489 CODEN: STSSE5
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: French
AB Recently, much interest has been focused on the significance of inducing not only systemic immunity, but also effective local immunity at susceptible mucosal surfaces. A new field of mucosal immunity has been established as information accumulates on mucosa-associated lymphoid tissue and on its role in both local and systemic immune responses. This article focuses directly on the use of microparticulate carriers to achieve effective mucosal immunization. The immunology of the mucosal immune system has been comprehensively reviewed elsewhere, and as such only key issues in conjunction with recent experiments which relate to mucosal immunization with microparticulate carriers will be addressed here.

L16 ANSWER 10 OF 17 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998131448 EMBASE
TITLE: Towards a multipurpose mucosal vaccination using phosphorylcholine as a unique **antigen**?.
AUTHOR: Trolle S.; Andremont A.; Fattal E.
CORPORATE SOURCE: E. Fattal, Lab. Physic. Pharmacotech. Biopharm., URA-CNRS 1218, Faculte de Pharmacie, 92296 Chatenay-Malabry Cedex, France
SOURCE: S.T.P. Pharma Sciences, (1998) 8/1 (19-30).
Refs: 112
ISSN: 1157-1489 CODEN: STSSE5
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: French
AB Intestinal and pulmonary bacterial infections are a major cause of worldwide child mortality. The development of a sole plurispecific vaccine against those infections is a World Health Organization

priority. In that respect, we hypothesized that immunization with phosphorylcholine, a ubiquitous **antigen** present on different pathogenic microorganisms, might be an original approach. Our vaccine is constituted of phosphorylcholine coupled to a protein carrier and entrapped in biodegradable microspheres. This vaccine is stable and adequate for oral or intranasal immunization and thus for the stimulation of the common mucosal immune system. Vaccinated animals were statistically protected against either a lethal oral challenge by Salmonella typhimurium, or a lethal nasal challenge by Streptococcus pneumoniae. The results constitute a strong impetus to explore the potentialities of our candidate vaccine.

L16 ANSWER 11 OF 17 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998036607 EMBASE
TITLE: Conference Science Medal 1997 lecture at British Pharmaceutical Conference, Scarborough, United Kingdom, September 15-18, 1997: Recent advances in vaccine adjuvants for systemic and mucosal administration.
AUTHOR: O'Hagan D.T.
CORPORATE SOURCE: D.T. O'Hagan, Chiron Corporation, 4560 Horton Street, Emeryville, CA 947608, United States
SOURCE: Journal of Pharmacy and Pharmacology, (1998) 50/1 (1-10).
Refs: 57
ISSN: 0022-3573 CODEN: JPPMAB
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Although vaccines produced by recombinant DNA technology are safer than traditional vaccines, which are based on attenuated or inactivated bacteria or viruses, they are often poorly immunogenic. Therefore, adjuvants are often required to enhance the immunogenicity of these vaccines. A number of adjuvants which are particulates of defined dimensions (< 5 .mu.m) have been shown to be effective in enhancing the immunogenicity of weak **antigens** in animal models. Two novel adjuvants which possess significant potential for the development of new vaccines include an oil-in-water microemulsion (MF59) and polymeric microparticles. MF59 has been shown to be a potent and safe adjuvant in human subjects with several vaccines (for example HSV-2, HIV-1 and influenza virus). An MF59 adjuvanted influenza has been recommended for approval in Italy. Microparticles prepared from the biode gradable

polymers the poly(**lactide**-co-glycolides) (**PLG**) are currently undergoing extensive pre-clinical evaluation as vaccine adjuvants. Because of their controlled release characteristics, microparticles also possess considerable potential for the development of single dose vaccines. The development of single dose vaccines would offer significant advantages and would improve vaccination uptake rates in at risk populations, particularly in the developing world. In addition to systemic administration, microparticles have also also been shown to enhance the immunogenicity of vaccines when administered by mucosal routes. Therefore microparticles may allow the development of novel vaccines which can be administered by non-parenteral routes. Mucosal administration of vaccines would significantly improve patient compliance by allowing immunization to be achieved without the use of needles. An alternative approach to the development of mucosally administered vaccines involves the production of genetically detoxified toxins. Heat labile enterotoxin (LT) from Escherichia coli and cholera toxin from Vibrio cholerae are two closely related bacterially produced toxins, which are the most potent adjuvants available. However, these molecules are too toxic to be used in the development of human vaccines. Nevertheless, these toxins have been modified by site-directed mutagenesis to produce molecules which are adjuvant active, but non-toxic. The most advanced of these molecules (LTK63), which has a single amino acid substitution in the enzymatically active subunit of LT, is active as an adjuvant, but non-toxic in pre-clinical models. The approach of genetically detoxifying bacterial toxins to produce novel adjuvants offers significant potential for the future development of mucosally administered vaccines.

L16 ANSWER 12 OF 17 MEDLINE DUPLICATE 1

| | |
|---|---|
| ACCESSION NUMBER: | 96351451 MEDLINE |
| DOCUMENT NUMBER: | 96351451 PubMed ID: 8717383 |
| TITLE: | Poly(lactide-co-glycolide) microencapsulation of vaccine **antigens**. |
| AUTHOR: | Jones D H; McBride B W; Farrar G H |
| CORPORATE SOURCE: | Microbial Antigens Department, Centre for Applied Microbiology and Research, Salisbury, Wilts, UK. |
| SOURCE: | JOURNAL OF BIOTECHNOLOGY, (1996 Jan 26) 44 (1-3) 29-36.<br>Journal code: AL6; 8411927. ISSN: 0168-1656. |
| PUB. COUNTRY: | Netherlands<br>Journal; Article; (JOURNAL ARTICLE) |
| LANGUAGE: | English |
| FILE SEGMENT: | B |
| ENTRY MONTH: | 199610 |
| ENTRY DATE: | Entered STN: 19961025<br>Last Updated on STN: 19961025 |

Searcher : Shears 308-4994

Entered Medline: 19961016

AB Fimbriae from Bordetella **pertussis** have been encapsulated in poly(**lactide**-co-glycolide) (**PLG**) microspheres of a size appropriate for oral administration. The binding of antibodies which react with conformational or linear fimbrial epitopes, to fimbriae released from microspheres, suggested that the process of was not detrimental to the native integrity of the protein. Mice were immunised by oral gavage with a single dose of microencapsulated fimbriae, or with fimbriae adsorbed onto alhydrogel and administered by intraperitoneal injection. The resulting immune responses in serum were comparable but only oral administration of microencapsulated fimbriae elicited specific immune responses in external secretions. Six weeks after immunisation, both groups of immunised animals were protected against challenge with live B. **pertussis**.

L16 ANSWER 13 OF 17 TOXLINE
ACCESSION NUMBER: 1996:1668 TOXLINE
DOCUMENT NUMBER: CRISP-96-AI33544-04
TITLE: MICROSPHERES TO ENHANCE VACCINE IMMUNOGENICITY.
AUTHOR: MICHALEK S M
CORPORATE SOURCE: UNIVERSITY OF ALABAMA, UAB STATION, ZRB 437, BIRMINGHAM, AL 35294-0007
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES.
CONTRACT NUMBER: 5R01AI33544-04
SOURCE: (1995). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199604

AB RPROJ/CRISP One of the major impediments to immunizing the world's children with a protective course of vaccinations against childhood diseases is the requirement for a complex course of booster immunizations. It has become clear that a significant proportion of this target population does not complete the full immunization regimen because of the number of clinic visits required. The primary goal of this proposal is to develop microencapsulated formulations of the current diphtheria, acellular **pertussis** , tetanus and Haemophilus influenza type B vaccines which will replace the pediatric vaccination series with a single injection at 2 months of age. The vaccines will be individually microencapsulated in **poly**(**DL-lactide** -co-**glycolide**)(DL- **PLG**), a biodegradable and biocompatible polyester which is approved for human use. Our

studies have shown that the delivery of protein and glycoprotein-based vaccines in DL-**PLG** microspheres strongly potentiates antibody responses. The antibody responses in mice to the microencapsulated vaccines will be measured by ELISA, and the protective efficacy of the responses tested in in vitro neutralization and bactericidal assays and in in vivo protection from lethal challenge studies. The biodegradation rate of DL-**PLGs** is determined by the ratio of **lactide** -to-glycolide in the copolymers. Thus, Vaccine-microspheres with different DL-**PLGs** release at different times after injection, and may be co-injected to deliver discrete pulses of vaccine which function as primary and booster immunizations. Each of the vaccines will be encapsulated in a series of DL-**PLGs** designed to release vaccine pulses which mimic the current 2, 4, 6 and 15-19 month immunization schedule after a single injection. The single injection pulse-release mixture of microencapsulated vaccines will be evaluated for appropriate booster responses, protective efficacy, absence of vaccine cross interference and stability with time and increased temperature.

L16 ANSWER 14 OF 17 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 95197236 MEDLINE
DOCUMENT NUMBER: 95197236 PubMed ID: 7890372
TITLE: Adjuvanticity and protective immunity elicited by Bordetella **pertussis antigens** encapsulated in **poly**(**DL-lactide**-co-**glycolide**) microspheres.
AUTHOR: Shahin R; Leef M; Eldridge J; Hudson M; Gilley R
CORPORATE SOURCE: Laboratory of Pertussis, Food and Drug Administration, Bethesda, Maryland 20892-4555.
SOURCE: INFECTION AND IMMUNITY, (1995 Apr) 63 (4) 1195-200. Journal code: GO7; 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950427
Last Updated on STN: 19950427
Entered Medline: 19950420

AB Purified Bordetella **pertussis antigens**, encapsulated in biodegradable **poly**(**DL-lactide**-co-**glycolide**) (DL-**PLG**) microspheres, were evaluated for their immunogenicity and ability to elicit a protective immune response against B. **pertussis** respiratory infection. Microencapsulated **pertussis** toxoid, filamentous hemagglutinin, and pertactin all retained their immunogenicity when administered parenterally. Intranasal

immunization with a low dose (1 micrograms) of encapsulated filamentous hemagglutinin, **pertussis** toxoid, or pertactin elicited strong specific immunoglobulin G and immunoglobulin A antibody responses in respiratory secretions that were greater in magnitude than the responses elicited by the same doses of unencapsulated **antigen**. Intranasal immunization with as little as 1 micrograms of encapsulated **pertussis antigen** prior to infection reduced the bacterial recovery by 3 log10 CFU. However, intranasal immunization with the same low doses of unencapsulated **antigens** did not reduce infection. Intranasal administration of a combination of 1 micrograms of each of the microencapsulated **pertussis antigens** was more effective in reducing bacterial infection than administration of any single microencapsulated **antigen**. Intranasal administration of microencapsulated B. **pertussis antigens** elicits high levels of specific antibody coinciding with protection against infection when these microspheres are administered to the respiratory tract. These data provide evidence of the respiratory adjuvanticity of three different DL-PLC microsphere preparations, each of which contains a unique B. **pertussis antigen**.

L16 ANSWER 15 OF 17 TOXLINE
ACCESSION NUMBER: 1995:205933 TOXLINE
DOCUMENT NUMBER: CRISP-95-AI33544-03
TITLE: MICROSPHERES TO ENHANCE VACCINE IMMUNOGENICITY.
AUTHOR: MICHALEK S M
CORPORATE SOURCE: UNIVERSITY OF ALABAMA, UAB STATION, ZRB 437, BIRMINGHAM, AL 35294-0007
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES.
CONTRACT NUMBER: 5R01AI33544-03
SOURCE: (1994). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199507
AB RPROJ/CRISP One of the major impediments to immunizing the world's children with a protective course of vaccinations against childhood diseases is the requirement for a complex course of booster immunizations. It has become clear that a significant proportion of this target population does not complete the full immunization regimen because of the number of clinic visits required. The primary goal of this proposal is to develop microencapsulated formulations of the current diphtheria, acellular **pertussis**

, tetanus and Haemophilus influenza type B vaccines which will replace the pediatric vaccination series with a single injection at 2 months of age. The vaccines will be individually microencapsulated in **poly**(**DL-lactide** -co-**glycolide**)(DL- **PLG**), a biodegradable and biocompatible polyester which is approved for human use. Our studies have shown that the delivery of protein and glycoprotein-based vaccines in DL-**PLG** microspheres strongly potentiates antibody responses. The antibody responses in mice to the microencapsulated vaccines will be measured by ELISA, and the protective efficacy of the responses tested in in vitro neutralization and bactericidal assays and in in vivo protection from lethal challenge studies. The biodegradation rate of DL-**PLGs** is determined by the ratio of **lactide** -to-glycolide in the copolymers. Thus, Vaccine-microspheres with different DL-**PLGs** release at different times after injection, and may be co-injected to deliver discrete pulses of vaccine which function as primary and booster immunizations. Each of the vaccines will be encapsulated in a series of DL-**PLGs** designed to release vaccine pulses which mimic the current 2, 4, 6 and 15-19 month immunization schedule after a single injection. The single injection pulse-release mixture of microencapsulated vaccines will be evaluated for appropriate booster responses, protective efficacy, absence of vaccine cross interference and stability with time and increased temperature.

L16 ANSWER 16 OF 17 TOXLINE
ACCESSION NUMBER: 1994:53540 TOXLINE
DOCUMENT NUMBER: CRISP-94-AI33544-02
TITLE: MICROSPHERES TO ENHANCE VACCINE IMMUNOGENICITY.
AUTHOR: MICHALEK S M
CORPORATE SOURCE: UNIVERSITY OF ALABAMA, UAB STATION, ZRB 437, BIRMINGHAM, AL 35294-0007
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES.
CONTRACT NUMBER: 5R01AI33544-02
SOURCE: (1993). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199403
AB RPROJ/CRISP One of the major impediments to immunizing the world's children with a protective course of vaccinations against childhood diseases is the requirement for a complex course of booster immunizations. It has become clear that a significant proportion of

this target population does not complete the full immunization regimen because of the number of clinic visits required. The primary goal of this proposal is to develop microencapsulated formulations of the current diphtheria, acellular **pertussis** , tetanus and Haemophilus influenza type B vaccines which will replace the pediatric vaccination series with a single injection at 2 months of age. The vaccines will be individually microencapsulated in **poly**(**DL-lactide** -co-**glycolide**)(DL- **PLG**), a biodegradable and biocompatible polyester which is approved for human use. Our studies have shown that the delivery of protein and glycoprotein-based vaccines in DL-**PLG** microspheres strongly potentiates antibody responses. The antibody responses in mice to the microencapsulated vaccines will be measured by ELISA, and the protective efficacy of the responses tested in in vitro neutralization and bactericidal assays and in in vivo protection from lethal challenge studies. The biodegradation rate of DL-**PLGs** is determined by the ratio of **lactide** -to-glycolide in the copolymers. Thus, Vaccine-microspheres with different DL-**PLGs** release at different times after injection, and may be co-injected to deliver discrete pulses of vaccine which function as primary and booster immunizations. Each of the vaccines will be encapsulated in a series of DL-**PLGs** designed to release vaccine pulses which mimic the current 2, 4, 6 and 15-19 month immunization schedule after a single injection. The single injection pulse-release mixture of microencapsulated vaccines will be evaluated for appropriate booster responses, protective efficacy, absence of vaccine cross interference and stability with time and increased temperature.

L16 ANSWER 17 OF 17 TOXLINE
ACCESSION NUMBER: 1994:53539 TOXLINE
DOCUMENT NUMBER: CRISP-94-AI33544-01
TITLE: MICROSPHERES TO ENHANCE VACCINE IMMUNOGENICITY.
AUTHOR: EDLRIDGE J H
CORPORATE SOURCE: UNIVERSITY OF ALABAMA, UAB STATION, ZRB 437, BIRMINGHAM, AL 35294-0007
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES.
CONTRACT NUMBER: 1R01AI33544-01
SOURCE: (1992). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199403

AB RPROJ/CRISP One of the major impediments to immunizing the world's children with a protective course of vaccinations against childhood diseases is the requirement for a complex course of booster immunizations. It has become clear that a significant proportion of this target population does not complete the full immunization regimen because of the number of clinic visits required. The primary goal of this proposal is to develop microencapsulated formulations of the current diphtheria, acellular **pertussis**, tetanus and Haemophilus influenza type B vaccines which will replace the pediatric vaccination series with a single injection at 2 months of age. The vaccines will be individually microencapsulated in **poly(DL-lactide-co-glycolide)**(DL- **PLG**), a biodegradable and biocompatible polyester which is approved for human use. Our studies have shown that the delivery of protein and glycoprotein-based vaccines in DL-**PLG** microspheres strongly potentiates antibody responses. The antibody responses in mice to the microencapsulated vaccines will be measured by ELISA, and the protective efficacy of the responses tested in in vitro neutralization and bactericidal assays and in in vivo protection from lethal challenge studies. The biodegradation rate of DL-**PLGs** is determined by the ratio of **lactide**-to-glycolide in the copolymers. Thus, Vaccine-microspheres with different DL-**PLGs** release at different times after injection, and may be co-injected to deliver discrete pulses of vaccine which function as primary and booster immunizations. Each of the vaccines will be encapsulated in a series of DL-**PLGs** designed to release vaccine pulses which mimic the current 2, 4, 6 and 15-19 month immunization schedule after a single injection. The single injection pulse-release mixture of microencapsulated vaccines will be evaluated for appropriate booster responses, protective efficacy, absence of vaccine cross interference and stability with time and increased temperature.

(FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, TOXLIT, TOXLINE, PHIC, PHIN' ENTERED AT 15:08:27 ON 04 JUN 2001)

L17 13 S BRAYDEN D?/AU AND (L4 OR L6 OR L7) Author

L18 7 DUP REM L17 (6 DUPLICATES REMOVED)

L18 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1

ACCESSION NUMBER: 2001:146645 CAPLUS

TITLE: Protection against Bordetella pertussis infection following parenteral or oral immunization with antigens entrapped in biodegradable particles: effect of formulation and route of immunization on induction of Th1 and Th2 cells

AUTHOR(S): Conway, M. A.; Madrigal-Estebas, L.; McClean,

S.; **Brayden, D. J.**; Mills, K. H. G.
CORPORATE SOURCE: Department of Biology, Institute of Immunology, Infection and Immunity Group, National University of Ireland, Maynooth, Ire.
SOURCE: Vaccine (2001), 19(15-16), 1940-1950
CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The immunogenicity and protective efficacy of systemically and orally delivered pertussis antigens entrapped in either microparticle poly-**lactide**-co-glycolide (**PLG**) or nanoparticle **PLG** formulations were evaluated in a murine respiratory challenge model for infection with Bordetella pertussis. The results demonstrate that immunization with two parenteral doses of 1 .mu.g or three oral doses of 100 .mu.g of pertussis toxoid (PTd) and filamentous haemagglutinin (FHA) encapsulated in PLG conferred a high level of protection against B. pertussis challenge. Furthermore protection could be generated with a single parenteral immunization with a combined microparticle and nanoparticle formulation. However, the route of immunization and the size of the particles affected the type of T cell response induced. Parenteral immunization with PTd and FHA entrapped in PLG microparticles elicits a potent type 1 T cell response and potent antibody response when given by the i.p. (i.p.) or i.m. (i.m.) route. In contrast, nanoparticle formulations favored the induction of Th2 cells.
REFERENCE COUNT: 39
REFERENCE(S):
(1) Ausiello, C; Infect Immun 1997, V65, P2168 CAPLUS
(2) Bazin, H; J Immunol 1970, V105, P1049 CAPLUS
(4) Bomford, R; AIDS Res Hum Retrovir 1992, V8, P1765 CAPLUS
(7) Cahill, E; Vaccine 1995, V13, P455 CAPLUS
(8) Challacombe, S; Immunology 1992, V76, P164 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
ACCESSION NUMBER: 2000:161163 CAPLUS
DOCUMENT NUMBER: 132:199032
TITLE: Method for inducing a cell-mediated immune response and parenteral vaccine formulations therefor
INVENTOR(S): **Brayden, David James**
PATENT ASSIGNEE(S): Elan Corporation, PLC, Ire.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000012125 | A1 | 20000309 | WO 1999-IE87 | 19990831 |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| AU 9954412 | A1 | 20000321 | AU 1999-54412 | 19990831 |

PRIORITY APPLN. INFO.: US 1998-98760 P 19980901
WO 1999-IE87 W 19990831

AB A method of inducing either a TH1 polarized immune response, a TH2 polarized immune response, or a combined TH1 and TH2 response to an antigen, and assocd. vaccine formulations, are disclosed. A method is provided for inducing a polarized TH1 response by parenteral administration of microparticles sized such that at least 50% of the microparticles are less than 5 .mu.m, the microparticles contg. antigen entrapped or encapsulated by a biodegradable polymer. Addnl., a method is provided for inducing a polarized TH2 response by parenteral administration of nanoparticles sized such that at least 50% of the nanoparticles are less than 600 nm, the nanoparticles contg. antigen entrapped or encapsulated by a biodegradable polymer. Vaccine formulations contg. the B. pertussis antigens PTd, FHA, or a combination of PTd and FHA, are provided.

REFERENCE COUNT: 11
REFERENCE(S):
(1) Cahill, E; VACCINE 1995, V13(5), P455 CAPLUS
(2) Cohen, S; "Microparticulate Systems for the Delivery of Proteins and Vaccines 1996, P51 CAPLUS
(3) Farrar Graham Henry; WO 9858668 A 1998 CAPLUS
(4) Jones, D; INFECTION AND IMMUNITY 1996, V64(2), P489 CAPLUS
(6) Medeva Holdings Bv; WO 9321950 A 1993 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
ACCESSION NUMBER: 2000:161162 CAPLUS
DOCUMENT NUMBER: 132:199031
TITLE: Oral vaccine compositions

INVENTOR(S): **Brayden, David James**
PATENT ASSIGNEE(S): Elan Corporation, PLC, Ire.
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000012124 | A1 | 20000309 | WO 1999-IE86 | 19990831 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9954411 | A1 | 20000321 | AU 1999-54411 | 19990831 |

PRIORITY APPLN. INFO.: US 1998-98759 P 19980901
WO 1999-IE86 W 19990831

AB Oral vaccine formulations are disclosed having microparticles sized such that at least 50% of the microparticles are less than 5 .mu.m, preferably less than 3 .mu.m, the microparticles contg. antigen entrapped or encapsulated, e.g. by a solvent evapn. method, by a biodegradable polymer, e.g. **poly(D,L-lactide-co-glycolide)**. Addnl., oral vaccine formulations are disclosed having nanoparticles sized such that at least 50% of the microparticles are less than 600 nm, preferably less than 500 nm, the nanoparticles contg. antigen entrapped or encapsulated, e.g. by a coacervation method, by a biodegradable polymer, e.g. **poly(D,L-lactide-co-glycolide)**. Protective vaccine formulations contg. the B. pertussis antigens PTd or a combination of PTd and FHA are provided.

REFERENCE COUNT: 9
REFERENCE(S):
(1) Cahill, E; VACCINE 1995, V13(5), P455 CAPLUS
(2) Desai, M; PHARMACEUTICAL RESEARCH 1996, V13(12), P1838 CAPLUS
(3) Henry, F; WO 9858668 A 1998 CAPLUS
(4) Jones, D; INFECTION AND IMMUNITY 1996, V64(2), P489 CAPLUS
(5) Medeva Holdings Bv; WO 9321950 A 1993 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 7 TOXLIT
ACCESSION NUMBER: 2000:8407 TOXLIT
DOCUMENT NUMBER: CA-132-199032J
TITLE: Method for inducing a cell-mediated immune response and parenteral vaccine formulations therefor.
AUTHOR: **Brayden DJ**
SOURCE: (2000). PCT Int. Appl. PATENT NO. 0012125 03/09/2000 (Elan Corporation, PLC).
CODEN: PIXXD2.
PUB. COUNTRY: IRELAND
DOCUMENT TYPE: Patent
FILE SEGMENT: CA
LANGUAGE: English
OTHER SOURCE: CA 132:199032
ENTRY MONTH: 200003
AB A method of inducing either a TH1 polarized immune response, a TH2 polarized immune response, or a combined TH1 and TH2 response to an antigen, and assocd. vaccine formulations, are disclosed. A method is provided for inducing a polarized TH1 response by parenteral administration of microparticles sized such that at least 50% of the microparticles are less than 5 .mu.m, the microparticles contg. antigen entrapped or encapsulated by a biodegradable polymer. Addnl., a method is provided for inducing a polarized TH2 response by parenteral administration of nanoparticles sized such that at least 50% of the nanoparticles are less than 600 nm, the nanoparticles contg. antigen entrapped or encapsulated by a biodegradable polymer. Vaccine formulations contg. the B. pertussis antigens PTd, FHA, or a combination of PTd and FHA, are provided.

L18 ANSWER 5 OF 7 TOXLIT
ACCESSION NUMBER: 2000:8406 TOXLIT
DOCUMENT NUMBER: CA-132-199031H
TITLE: Oral vaccine compositions.
AUTHOR: **Brayden DJ**
SOURCE: (2000). PCT Int. Appl. PATENT NO. 0012124 03/09/2000 (Elan Corporation, PLC).
CODEN: PIXXD2.
PUB. COUNTRY: IRELAND
DOCUMENT TYPE: Patent
FILE SEGMENT: CA
LANGUAGE: English
OTHER SOURCE: CA 132:199031
ENTRY MONTH: 200003
AB Oral vaccine formulations are disclosed having microparticles sized such that at least 50% of the microparticles are less than 5 .mu.m, preferably less than 3 .mu.m, the microparticles contg. antigen entrapped or encapsulated, e.g. by a solvent evapn. method, by a biodegradable polymer, e.g. **poly**(**D**,**L**-

**lactide**-co-**glycolide**). Addnl., oral vaccine formulations are disclosed having nanoparticles sized such that at least 50% of the microparticles are less than 600 nm, preferably less than 500 nm, the nanoparticles contg. antigen entrapped or encapsulated, e.g. by a coacervation method, by a biodegradable polymer, e.g. **poly**(**D**,**L**-**lactide**-co-**glycolide**). Protective vaccine formulations contg. the B. pertussis antigens PTd or a combination of PTd and FHA are provided.

L18 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
ACCESSION NUMBER: 1999:722187 CAPLUS
DOCUMENT NUMBER: 132:255890
TITLE: Protection against B. pertussis challenge following parenteral and oral administration of microparticles loaded with pertussis antigens
AUTHOR(S): McClean, S.; Conway, M.; Mills, K. H. G.; **Brayden, D. J.**
CORPORATE SOURCE: Elan Pharmaceutical Technologies, Dublin, 2, Ire.
SOURCE: Proc. Int. Symp. Controlled Release Bioact. Mater. (1999), 26th, 153-154
CODEN: PCRMEY; ISSN: 1022-0178
PUBLISHER: Controlled Release Society, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Administration of pertussis toxin and filamentous hemagglutinin entrapped in glycolide-**lactide** copolymer (**PLG**) microparticles provides protective immunity after either oral or parenteral immunization. I.p. immunization with PLG-entrapped antigens resulted in a distinct TH1 response, which has the potential for the development of vaccines against dieases caused by intracellular organisms.
REFERENCE COUNT: 4
REFERENCE(S): (1) Mills; Infect Immun 1993, V61, P339
(2) Mills; Infect Immun 1997, V66, P594
(3) Moore; Vaccine 1995, V13, P1741 CAPLUS
(4) Ramtoola; J Microencap 1992, V9, P415 CAPLUS

L18 ANSWER 7 OF 7 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998119382 EMBASE
TITLE: Binding and uptake of biodegradable poly-DL-lactide micro- and nanoparticles in intestinal epithelia.
AUTHOR: McClean S.; Prosser E.; Meehan E.; O'Malley D.; Clarke N.; Ramtoola Z.; **Brayden D.**
CORPORATE SOURCE: S. McClean, Elan Pharmaceutical Technologies, Biotechnology Building, Trinity College, Dublin 2, Ireland

Searcher : Shears 308-4994

SOURCE: European Journal of Pharmaceutical Sciences, (1998) 6/2 (153-163).
Refs: 30
ISSN: 0928-0987 CODEN: EPSCED
PUBLISHER IDENT.: S 0928-0987(97)10007-0
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
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AB The use of biodegradable particles as oral delivery vehicles for macromolecular drugs was investigated. We evaluated the binding, uptake and absorption of poly-DL-lactide (PLA) micro- and nanoparticles in Caco-2 monolayers and in ileal tissue and gut associated lymphoid tissue (GALT) of anaesthetised rats and rabbits. Using a range of experimental techniques, we found that approximately 10% of administered micro- and nanoparticles were adsorbed to the apical membranes of each of the five intestinal models. Nanoparticles were found to be absorbed better than microparticles. Overall, little discrimination in uptake patterns was evident between Peyer's patch (PP) and non-PP tissue while rat ileum showed a greater uptake capacity than rabbit. Our results show that uptake of PLA particles was low capacity, size- dependent and predominantly transcellular in all systems. A low proportion of the apically-bound particles was absorbed, with uptake exclusion evident for particles >4.mu.m. The affinity of PLA particles for intestinal epithelia and GALT needs to be greatly enhanced in order to achieve improved oral bioavailability of macromolecules.